## Response

Claims 1-44 are pending. Claims 1-44 are rejected. No claim has been amended or canceled.

## Response to Claim Rejections Based on 35 USC § 103(a)

Claims 1-44 are rejected as being unpatentable over the combined teachings of JP-3-56415 and US 6,602,911 (Kranzler *et al.*) for the reasons of record. The Examiner argues in the instant Office Action that it "is well known in the chemical art that enantiomers are obvious over racemates, absent evidence to the contrary." The Examiner then asserts that the Applicants have not submitted any unexpected results of the claimed enantiomers. The Applicants respectfully disagree with this assertion.

*Cellular Assay Results*

(±)-*para*-Hydroxy-milnacipran, (–)-*para*-hydroxy-milnacipran and (+)-*para*-hydroxy-milnacipran were evaluated for inhibition of cellular norepinephrine uptake and serotonin uptake; and some of the data obtained was provided in the instant application (*e.g.*, page 19, lines 19-27; and Figure 61). For clarity the activity data is also tabulated below (Table 1). Please note that therein "N" represents norepinephrine uptake; and "S" represents serotonin uptake.

**Table 1**

| compound | $IC_{50}$ (nM) | |
|---|---|---|
| | N | S |
| (±)-*para*-hydroxy-milnacipran | 28.6 | 21.7 |
| (+)-*para*-hydroxy-milnacipran (**A**) | 10.3 | 22.0 |
| (–)-*para*-hydroxy-milnacipran (**B**) | 88.5 | 40.3 |

Cursory inspection reveals that the racemate and enantiomers have distinct biological-activity profiles. Below the Applicants compare the specific $IC_{50}$ values to reinforce their

assertion that the enantiomers are patentable over the racemate due to their unexpected characteristics.

Shown below in Table 2 is a comparison of the inhibition of norepinephrine uptake by the (+)-enantiomer and the racemate.

**Table 2**

| |
|---|
| ratio 1 = inhibition of norepinephrine uptake by (±)-*para*-hydroxy-milnacipran / inhibition of norepinephrine uptake by (+)-*para*-hydroxy-milnacipran<br>= 28.6 nM / 10.3 nM<br>= **2.8** |

Ratio 1 establishes that the (+)-enantiomer is a much better inhibitor of norepinephrine uptake than the racemate. Specifically, the (+)-enantiomer is *2.8 time more active* than the racemate at inhibiting the uptake of norepinephrine. One of skill in the art would not have been able to predict that the (+)-enantiomer would be so active in inhibiting norepinephrine uptake.

In addition, as highlighted by the three additional comparisons shown below in Table 3, the relative selectivities of the (+)-enantiomer and the racemate are unexpectedly great for the inhibition of norepinephrine uptake.

**Table 3**

| |
|---|
| ratio 2 = inhibition of norepinephrine uptake by (±)-*para*-hydroxy-milnacipran / inhibition of serotonin uptake by (±)-*para*-hydroxy-milnacipran<br>= 28.6 nM / 21.7 nM<br>= **1.3** |
| ratio 3 = inhibition of norepinephrine uptake by (+)-para-hydroxy-milnacipran / inhibition of serotonin uptake by (+)-para-hydroxy-milnacipran<br>= 10.3 nM / 22.0 nM<br>= **0.5** |
| ratio 4 = ratio 2 / ratio 3<br>= 1.3 / 0.5<br>= **2.6** |

As shown above, ratio 4 compares ratio 2 (the ratio of the activities of the racemate for inhibiting norepinephrine and serotonin uptake, respectively) with ratio 3 (the ratio of activities of the (+)-enantiomer for inhibiting norepinephrine and serotonin uptake, respectively). Notably, ratio 4

establishes that the (+)-enantiomer is actually a 2.6 times more selective inhibitor of norepinephrine uptake over serotonin uptake, compared to the racemate. Again, it would not have been obvious to one of ordinary skill in the art that the (norepinephrine uptake)/(serotonin uptake) selectivity of the (+)-enantiomer would be substantially different than that of the racemate.

Furthermore, the Applicants respectfully assert that Examiner has failed to appreciate that the non-obviousness of the instant invention is not solely due to a factor of "degree", but it is, quite remarkably and unexpectedly, due to a difference in "kind". *See In re Huang*, 100 F.3d 135, 139 (Fed Cir 1996). Namely, at the filing date of the application, one skilled in the relevant art would not have predicted, given that the racemic compound is a *non-selective* inhibitor of norepinephrine and serotonin uptake (see ratio 2 above), that the individual enantiomers of para-hydroxy-milnacipran would be *selective* inhibitors of norepinephrine and serotonin uptake. Moreover, even more remarkably in some regards, one of the enantiomers is 2.2 times more selective for norepinephrine uptake while the other enantiomer proves to be 2.1 times more selective for serotonin uptake (Table 4). In other words, given the lack of specificity associated with the known racemic mixture, the fact that each enantiomer shows greater than 2.0 times the selectivity at *different* sites (inhibition of norepinephrine and serotonin uptake) is quite remarkable.

**Table 4**

| | |
|---|---|
| ratio 5 | = inhibition of norepinephrine uptake by (-)-*para*-hydroxy-milnacipran / inhibition of serotonin uptake by (-)-*para*-hydroxy-milnacipran<br>= 88.5 nM / 40.3 nM<br>= **2.2** |
| ratio 6 | = inhibition of serotonin uptake by (+)-*para*-hydroxy-milnacipran / inhibition of norepinephrine uptake by (+)-*para*-hydroxy-milnacipran<br>= 22.0 nM / 10.3 nM<br>= **2.1** |

In vitro *Assay Results*

(±)-*para*-Hydroxy-milnacipran, (–)-*para*-hydroxy-milnacipran and (+)-*para*-hydroxy-milnacipran were also evaluated in competitive radioligand *in vitro* binding assays of norepinephrine binding sites and serotonin binding sites; and some of the data obtained was

provided in the instant application (*e.g.*, page 19, lines 11-18; and Figures 59 and 60). For clarity the activity data is also tabulated below (Table 5). Please note that therein "N" represents norepinephrine uptake; and "S" represents serotonin uptake.

**Table 5**

| compound | $K_i$ (nM) | |
|---|---|---|
| | N | S |
| (±)-*para*-hydroxy-milnacipran | 218 | 6.73 |
| (+)-*para*-hydroxy-milnacipran (**A**) | 112 | 3.88 |
| (–)-*para*-hydroxy-milnacipran (**B**) | 1,680 | 8.15 |

Once again, even cursory inspection reveals that the racemate and enantiomers have distinct biological-activity profiles. The Applicants respectfully contend that the *in vitro* data further reinforce their assertion that the enantiomers are patentable over the racemate due to their unexpected characteristics.

Accordingly, the Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1-44 based on 35 USC § 103(a).

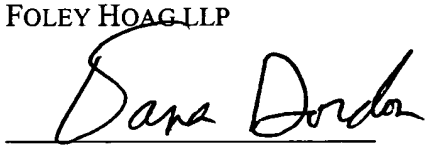
## Fees

The Applicants believe no fee is required in connection with the filing of this paper. Nevertheless, the Director is hereby authorized to charge any required fee to our Deposit Account, **06-1448**; Reference **CPX-003.01**.

## Conclusion

In view of the above amendments and remarks, it is believed that the pending claims are in condition for allowance. The Applicants respectfully request reconsideration and withdrawal of the pending rejections. The Applicants thank the Examiner for careful consideration of the present case. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to contact the undersigned.

Respectfully submitted,
FOLEY HOAG LLP



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